FOUNDATIONONE® CDx

Beispielbericht

Lungenkrebs

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https://go.roche.com/USZ-molekulares-tumorprofiling

USZ Universitäts Spital Zürich

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FOUNDATIONONE®CDx

PATIENT XXXX

TUMOR TYPE Lung adenocarcinoma

COUNTRY CODE CH

REPORT DATE XXXX

USZ# XXXX

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT

DISEASE Lung adenocarcinoma
NAME XXXX
DATE OF BIRTH XXXX 1945
SEX Male
MEDICAL RECORD # XXXX

PHYSICIAN

ORDERING PHYSICIAN USZ, Pathologie
MEDICAL FACILITY Institut fuer Pathologie und Molekularpatholgie
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 201897
PATHOLOGIST ,

SPECIMEN

SPECIMEN SITE Lung
SPECIMEN ID XXXX
SPECIMEN TYPE FFPE
DATE OF COLLECTION Invalid date
SPECIMEN RECEIVED XXXX

Genomic Signatures

Microsatellite status - MS-Stable
Tumor Mutational Burden - 8 Muts/Mb

Gene Alterations

For a complete list of the genes assayed, please refer to the Appendix.

CD274 (PD-L1) amplification
PDCD1LG2 (PD-L2) amplification
MAP2K1 (MEK1) amplification - equivocal†
PTEN loss exons 1-7
CRKL amplification
JAK2 amplification
MLL2 P1011fs*6
MUTYH G382D
NOTCH1 R1114fs*65
TP53 R248L

8 Disease relevant genes with no reportable alterations: ***ALK, BRAF, EGFR, ERBB2, KRAS, MET, RET, ROS1***

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Atezolizumab** (p. 11), **Cemiplimab** (p. 15), **Durvalumab** (p. 12), **Nivolumab** (p. 13), **Nivolumab + Ipilimumab** (p. 16), **Pembrolizumab** (p. 14)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 17)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***MUTYH*** **G382D** (p. 8)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***MLL2*** **P1011fs*6** (p. 8)

GENOMIC SIGNATURES	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Genomic Signatures section
Tumor Mutational Burden - 8 Muts/Mb	**No therapies or clinical trials.** see Genomic Signatures section

GENE ALTERATIONS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
CD274 (PD-L1) - amplification	Atezolizumab 1 Durvalumab 1 Nivolumab 1 Pembrolizumab 1	Cemiplimab 1 Nivolumab + Ipilimumab 1 Avelumab
10 Trials *see p. 17*		
PDCD1LG2 (PD-L2) - amplification	Atezolizumab 1 Durvalumab 1 Nivolumab 1 Pembrolizumab 1	Cemiplimab 1 Avelumab
10 Trials *see p. 21*		
MAP2K1 (MEK1) - amplification - equivocal	none	none
10 Trials *see p. 19*		
PTEN - loss exons 1-7	none	none
10 Trials *see p. 23*		

☐ *NCCN category*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.

MUTYH - G382D ..... p. 8

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

MLL2 - P1011fs*6 ..... p. 8

GENE ALTERATIONS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Gene Alterations section.

NOTE Genomic alterations detected may be associated with activity of certain drugs approved by applicable regulatory authorities (for example, the FDA, EMA, or country specific regulatory authorities); however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report includes scientific information. Foundation Medicine's genetic test and this genetic test report, including the information on therapies and clinical trials contained in this report, should not be used as the single basis for the therapy decision. The report should only be regarded and used as a supplementing source of information: All treatment decisions remain the full and final responsibility of the respective treating physician. For various reasons further explained below, both the therapies and the clinical trials listed in this report may not be complete and exhaustive. All drugs displayed in the report have been approved by Swissmedic, but not necessarily in the patient's tumor type. Please find the entire Swiss Prescribing Information on www.swissmedicinfo.ch.

GENOMIC SIGNATURE

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[6-11], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[12-15]. One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[6]. Published data investigating the prognostic implications of MSI in NSCLC are limited (PubMed, Oct 2021).

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[16]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[16-18]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[19-21]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16,18,20-21].

GENOMIC SIGNATURE

Tumor Mutational Burden

RESULT
8 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-31]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors or combination of PD-1 and CTLA-4 inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb (based on this assay or others); similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb (based on this assay or others);[22-23,26-28,32-39]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[40], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[41], has been observed across all TMB levels.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[42]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[43]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[44-45], several other large studies did find a strong association with increased TMB[46-49]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[50]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[44]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[51]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[51-52].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[53-54] and cigarette smoke in lung cancer[32,55], treatment with temozolomide-based chemotherapy in glioma[56-57], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[58-62], and microsatellite instability (MSI)[58,61-62]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[22-23,26-28,32-39,63].

GENE

CD274 (PD-L1)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of strong clinical evidence, CD274 amplification and PD-L1 overexpression may predict sensitivity to antibodies targeting PD-L1 or PD-1. Patients with high tumor PD-L1 expression across multiple solid tumor types have exhibited improved OS with the PD-L1 antibody atezolizumab[64-65]. Compared with PD-L1-negative patients, clinical studies with the PD-L1 antibody durvalumab have suggested higher response rates for patients with PD-L1-positive tumor or immune cells and urothelial carcinoma[66], non-small cell lung cancer (NSCLC)[67-68] , or head and neck squamous cell carcinoma[69-70] . The PD-1 antibodies pembrolizumab and nivolumab (alone or in combination with ipilimumab) have elicited significant clinical responses in solid tumors[71-73], and for patients with Hodgkin lymphoma, a tumor type that harbors frequent PD-L1 copy number gains[74]. Clinical studies have reported that PD-L1 amplification[71] or expression[75] in solid tumors is associated with response to anti-PD-1 antibodies. However, a study evaluating nivolumab in patients with urothelial carcinoma observed no correlation between OS benefit and PD-L1 expression levels[76]. A Phase 1 trial evaluating bintrafusp alfa, a fusion protein targeting TGF-beta and PD-L1, in the second line setting for patients with NSCLC reported ORRs of 36% (10/27) and 86% (6/7) for patients with PD-L1-positive and PD-L1-high expression, respectively[77]. JAK2 has been reported as important for PD-L1 expression in Hodgkin lymphoma and primary mediastinal B-cell lymphoma cell lines, and JAK2 inhibition has been reported to decrease PD-L1 transcript accumulation[78-79]. Therefore, JAK2 inhibitors such as ruxolitinib may also be relevant for a patient with PD-L1 amplification.

FREQUENCY & PROGNOSIS

CD274 amplification has been reported in 1-2% of cases in the Lung Adenocarcinoma and Lung Squamous Cell Carcinoma TCGA datasets[80-81]. Higher PD-L1 expression in non-small cell lung cancer (NSCLC) has been correlated with poor patient prognosis in multiple studies[82-84].

FINDING SUMMARY

CD274 encodes the programmed cell death ligand 1 (PD-L1), also known as B7-H1, which is a cell surface molecule important for regulating the activity of T-cells through binding to various T-cell receptors. Although PD-L1 is a costimulatory molecule for naive T-cells, it can provide inhibitory signals to activated T-cells through interactions with the receptors PD-1 or CD80[85-86]. These signals can help PD-L1-expressing tumor cells evade immune detection by natural killer cells or T-cells[87-89]. CD274 amplification is associated with positive PD-L1 protein expression in solid tumors[90-92] and lymphomas[74,78].

GENE

PDCD1LG2 (PD-L2)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PDCD1LG2 amplification, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-1, PD-L1, or PD-L2 antibodies. The PD-1 antibodies pembrolizumab and nivolumab have elicited significant clinical responses in several cancer types, including melanoma, NSCLC, renal cell carcinoma[93-101], and Hodgkin lymphoma, which harbors frequent PD-L2 copy number gains[74,102]. The PD-L1 antibody atezolizumab does not block interaction between PD-1 and PD-L2; however, multiple clinical studies with atezolizumab have reported an association between increased PD-L2 expression and response or improved overall survival in multiple solid tumor types, thereby suggesting that PD-L2 overexpression may serve as a biomarker of response[64-65,103]. Additionally, JAK2 has been reported as important for PD-L2 expression in Hodgkin lymphoma and PMBCL cell lines, and JAK2 inhibition has been reported to decrease PD-L2 transcript accumulation in preclinical studies[78-79]. Therefore, JAK2 inhibitors may also be relevant for a patient with PD-L2 amplification. Ruxolitinib is a kinase inhibitor that targets JAK1 and JAK2 and is approved to treat intermediate or high-risk myelofibrosis[104].

FREQUENCY & PROGNOSIS

In the TCGA datasets, PDCD1LG2 amplification was observed in 3% of lung squamous cell carcinoma (SCC) cases[81] and <1% of cases in the Lung Adenocarcinoma TCGA dataset[80]. PD-L2 was found to be expressed in approximately 50% of lung adenocarcinoma tumors and to predict poor overall survival, independently of PD-L1 expression[105]. PD-L2 protein expression was observed in 24% of pulmonary SCC samples and expression was more frequent (93.5%) in metastatic lymph node tumors; PD-L2 expression was not significantly associated with prognosis in this study[106].

FINDING SUMMARY

PDCD1LG2 encodes the programmed cell death 1 ligand 2 (PD-L2), also known as CD273, PD-L2, and B7-DC, which is essential for T-cell proliferation and interferon production. PD-1 signaling, which can be stimulated by PD-L2, results in 'T-cell exhaustion', a temporary inhibition of activation and proliferation that can be reversed on removal of the PD-1 signal[85-86]. Amplification of PDCD1LG2 and the adjacent locus CD274, encoding PD-L1, has been reported in 29% of primary mediastinal B-cell lymphoma (PMBCL) cases, and PDCD1LG2 copy number gain has been reported to correlate with increased PD-L2 protein expression as determined by immunohistochemistry[107-108].

GENE

MAP2K1 (MEK1)

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and clinical data suggest that activating alterations in MAP2K1 may predict sensitivity to MEK inhibitors[109-114] such as cobimetinib, trametinib, and selumetinib.

FREQUENCY & PROGNOSIS

MAP2K1 amplification has been reported in fewer than 1% cases in the Lung Adenocarcinoma and Lung Squamous Cell Carcinoma TCGA datasets[80-81]. MAP2K1 mutation has been reported in 1% of cases analyzed in the lung adenocarcinoma[80] and lung squamous cell carcinoma[81] TCGA datasets, and in up to 3% of non-small cell lung cancer (NSCLC) cases in the scientific literature[112,115-119]. Overall survival rates for patients with lung adenocarcinoma harboring activating MAP2K1 mutations were similar to those with mutations in KRAS or BRAF, but were significantly reduced compared to those with EGFR mutations or rearrangements involving ALK, RET, or ROS1[120].

FINDING SUMMARY

MAP2K1 (also known as MEK1) encodes the signaling protein mitogen-activated protein kinase kinase 1 (MKK1 or MEK1). MEK1 phosphorylates the ERK1/2 proteins in the RAS-RAF-MAP kinase pathway, a critical pathway in processes of cell division and differentiation[121]. MAP2K1 has been reported to be amplified in cancer[122] and may be biologically relevant in this context[123-124].

GENE

PTEN

ALTERATION
loss exons 1-7

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[125-128]. Across various tissues, most clinical studies have not observed an association between PTEN deficiency and response to inhibitors of the PI3K-AKT-mTOR pathway. However, limited studies in prostate cancer[129-132], renal cell carcinoma[133], breast cancer[134-135], and colorectal cancer[136] have reported an association between PTEN deficiency and response to inhibitors targeting the PI3K-AKT-mTOR pathway. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[137-141], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[142], ovarian cancer[143], uterine leiomyosarcoma[144], and endometrial cancer[141] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[145-146].

FREQUENCY & PROGNOSIS

Studies have reported PTEN mutation in 4.5% of non-small cell lung cancer (NSCLC) cases[147], with higher incidence reported in lung squamous cell carcinoma (10-11%)[81,147] compared with lung adenocarcinoma (1-2.5%)[47-48,80,147]. PTEN loss has been reported in 9.9% of lung SCC and <1% of lung NSCLC cases[122,148]. Loss of PTEN expression by IHC was reported in up to 35% of NSCLC cases in one study, with several studies reporting more frequent loss of PTEN in squamous cell lung carcinoma compared to lung adenocarcinoma[149-152]. Loss of PTEN protein expression has been identified as a marker of poor prognosis in NSCLC[149,151].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[126]. Alterations such as seen here may disrupt PTEN function or expression[153-194].

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[195-196]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[195,197]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[195]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
CRKL

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that directly target CRKL[198-199]. Preclinical studies report that some cancer cell lines with CRKL amplification are sensitive to tyrosine kinase inhibitor (TKI) dasatinib[198-200]. However, a patient with CRKL-amplified pancreatic cancer did not respond to dasatinib[201]. CRKL amplification has been shown to be a mechanism of acquired resistance to EGFR TKIs[199,202].

FREQUENCY & PROGNOSIS

CRKL amplification has been identified in various solid tumor types, including uterine carcinosarcoma (7%), pancreatic ductal adenocarcinoma (5.5%)[203], lung squamous cell carcinoma (4.5%)[81], sarcoma (4%), ovarian serous cystadenocarcinoma (3%), bladder urothelial carcinoma (3%)[204], and melanoma (2%)(cBioPortal, 2022)[122,148]. Increased CRKL expression has been reported in many tumor types, including lung[205-206], breast[207-208], ovarian[208-209], pancreatic[210], skin[208], colon[208,211], hepatocellular[212], and gastric cancers[198]. CRKL overexpression has been shown to significantly correlate with reduced OS for patients with NSCLC or hepatocellular carcinoma[206,212] and with tumor size and metastasis for patients with breast cancer[207].

FINDING SUMMARY

CRKL encodes an adaptor protein that has been shown to mediate growth, motility, and adhesion in solid tumor cells[213]. Studies in non-small cell lung cancer (NSCLC) and pancreatic cancer cells have linked CRKL amplification and overexpression with increased cell proliferation and with tumorigenesis[199,205-206,210].

GENE
JAK2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

While JAK2 inhibitors have shown clinical benefit in hematological malignancies, clinical utility in solid tumors has not been demonstrated.

FREQUENCY & PROGNOSIS

Amplification of JAK2 has rarely been reported in lung cancer, detected in 2% and 1% in the lung adenocarcinoma and lung squamous cell carcinoma TCGA datasets, respectively[80-81]. Increased expression and activity of JAK2 has been reported in non-small cell lung cancer (NSCLC), cited in 57-79% of cases, and has been correlated with activation of the STAT3 pathway[214-215]. High expression of the JAK2-STAT3 pathway has been associated with decreased survival in patients with NSCLC[215].

FINDING SUMMARY

JAK2 encodes Janus kinase 2, a tyrosine kinase that regulates signals triggered by cytokines and growth factors[216]. JAK2 is often mutated in hematopoietic and lymphoid cancers. Cell lines and primary lymphoid cancer cells from a small number of patients with JAK2 amplification exhibit overabundance of JAK2 mRNA, protein, and phosphorylated JAK2 targets and respond to JAK2 inhibitors such as ruxolitinib similarly to JAK2-rearranged (activated) cell lines and primary blood cells from patients[78,217].

GENE
MLL2

ALTERATION
P1011fs*6

TRANSCRIPT ID
NM_003482

CODING SEQUENCE EFFECT
3032delC

VARIANT ALLELE FREQUENCY (% VAF)
16.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in MLL2.

FREQUENCY & PROGNOSIS

MLL2 alterations are observed in a number of solid tumor contexts (COSMIC, Jan 2022)[218], and are especially prevalent in lung squamous cell carcinoma (SCC)[81] and small cell lung carcinoma (SCLC)[219]. MLL2 mutation was found to be an independent prognostic factor of poor PFS and OS in non-small cell lung cancer, but not in SCLC[220]. One study reported that MLL2 truncating mutations were more common in recurrent ovary granulosa cell tumors (GCT) compared with primary GCTs (24% [10/42] vs. 3.0% [1/32])[221]. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS[222].

FINDING SUMMARY

MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[223]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[224]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[225].

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[226-231]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[230,232-233]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
MUTYH

ALTERATION
G382D

TRANSCRIPT ID
NM_001048171

CODING SEQUENCE EFFECT
1145G>A

VARIANT ALLELE FREQUENCY (% VAF)
29.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies or clinical trials available to address MUTYH alterations in cancer.

FREQUENCY & PROGNOSIS

In general, somatic MUTYH mutations are infrequently reported across cancer types (COSMIC, 2022)[218]. Monoallelic MUTYH mutation occurs in 1-2% of the general population[234-235]. There is conflicting data regarding the impact of monoallelic mutations on the risk of developing CRC[236-238]. Patients with MUTYH-mutant CRC were reported to have significantly improved overall survival compared to patients without MUTYH mutation[239].

FINDING SUMMARY

MUTYH (also known as MYH) encodes an enzyme involved in DNA base excision repair, and loss of function mutations in MUTYH result in increased rates of mutagenesis and promotion of tumorigenesis[240]. The two most frequently reported MUTYH loss of function mutations are G382D (also referred to as G396D) and Y165C (also referred to as Y179C)[234-235,241-243]. Numerous other MUTYH mutations have also been shown to result in loss of function[241-244].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the MUTYH variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with MUTYH-associated polyposis (ClinVar, Sep 2021)[245]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline biallelic MUTYH mutation causes MUTYH-associated polyposis (also known as MYH-associated polyposis or MAP), an autosomal recessive condition characterized by multiple colorectal adenomas and increased lifetime risk of colorectal cancer (CRC)[234,246-248]. MAP accounts for approximately 0.7% of all CRC cases and 2% of early-onset CRC cases[234]. In contrast to CRC, the role of MUTYH mutation in the context of other cancer types is not well established[249-253]. Estimates for the prevalence of MAP in the general population range from 1:5,000-1:10,000[235]. Therefore, in the appropriate clinical context, germline testing of MUTYH is recommended.

GENE
NOTCH1

ALTERATION
R1114fs*65

TRANSCRIPT ID
NM_017617

CODING SEQUENCE EFFECT
3340delC

VARIANT ALLELE FREQUENCY (% VAF)
47.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

NOTCH1 inhibitors and gamma-secretase inhibitors (GSIs) may be potential therapeutic approaches in the case of NOTCH1 activating mutations[254-262]. In a Phase 2 study, the GSI AL101 (BMS-906024) elicited PRs in 15% (6/39) and SDs in 54% (21/39) of patients with metastatic adenoid cystic carcinoma (ACC) harboring NOTCH activating alterations[263]. Additional responses to AL101 have been reported in a patient with gastroesophageal junction adenocarcinoma harboring multiple NOTCH1 mutations, a patient with T-cell acute lymphoblastic leukemia (T-ALL) harboring a NOTCH1 HD domain mutation, and a patient with ACC harboring a single NOTCH1 mutation[264]. A Phase 1 study of the pan-NOTCH inhibitor CB-103 for patients with advanced or recurrent solid tumors reported a preliminary mPFS of 21.7 weeks for patients with ACC, with 2 patients harboring NOTCH1-mutated ACC demonstrating SD > 6 months as best response[265]. On the basis of clinical data in non-Hodgkin lymphoma, NOTCH1 activating alterations may be associated with sensitivity to the approved PI3K inhibitor copanlisib[266]; this is further supported by limited preclinical data that suggest that NOTCH1 may be a negative regulator of PTEN[267-268]. A study of several cohorts of patients with NSCLC reported an association between deleterious NOTCH mutations (NOTCH1-3 considered as a pooled set) and improved clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors[269]. However, as presence of NOTCH mutation correlates with higher TMB, the independent predictive power of NOTCH alterations is not entirely clear; furthermore, significant associations with improved clinical benefit were not found for mutations in NOTCH1, NOTCH2, or NOTCH3 considered individually, and the study did not delineate clinical associations for different types of NOTCH alterations[269]. Therefore, it is unclear if the alteration seen here would predict efficacy of treatment with an immune checkpoint inhibitor. While activating mutations may be targeted via gamma-secretase inhibitors or PI3K inhibitors, there are no therapies available to address NOTCH1 inactivation, as seen here.

FREQUENCY & PROGNOSIS

Mutation of NOTCH1 has been reported in 4% and 7% of cases, respectively, in the Lung Adenocarcinoma and Lung Squamous Cell Carcinoma TCGA datasets; homozygous loss of NOTCH1 was not reported[80-81]. While NOTCH inactivation or loss in non-small cell lung cancer (NSCLC) has rarely been described in the literature, one study reported that 12% (6/49) of NSCLC samples harbored activating NOTCH1 mutations and another reported that NOTCH1 is overexpressed in NSCLC[270-271]. A study of 441 patients with lung adenocarcinoma correlated increased NOTCH activity with poor clinical outcome; HES1 overexpression, a direct target of NOTCH, also correlated with poor overall survival in an independent study of 89 patients with adenocarcinoma[270,272]. NOTCH1 overexpression has been correlated with poor patient survival rates in patients with NSCLC[273]. Activation of the NOTCH1 pathway through cisplatin-induced NOTCH1 expression has been reported to be associated with multidrug resistance in lung adenocarcinoma cells[274].

FINDING SUMMARY

NOTCH1 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or an oncogene[275-276]. Upon binding of membrane-bound ligands, the NOTCH1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex that regulates downstream target genes involved in cell fate determination, proliferation, and apoptosis[277-278]. NOTCH1 alterations that disrupt ligand binding[279-281] or remove the transmembrane domain (amino acids 1736-1756), RAM domain (amino acids 1757-1926), ankyrin repeats (amino acids 1927-2122) and/or transactivation domain (amino acids 2123-2374) that are necessary for NOTCH1 function, such as observed here, are predicted to be inactivating[278,282-284]. Several point mutations, including D469G, A465T, C478F, R1594Q, and P1770S, have also been reported to inactivate NOTCH1[275,285-286].

GENE
TP53

ALTERATION
R248L

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
743G>T

VARIANT ALLELE FREQUENCY (% VAF)
48.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[287-290], or p53 gene therapy and immunotherapeutics such as SGT-53[291-295] and ALT-801[296]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[297]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[298]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[299]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[300]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[301]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[302]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[303]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[295]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[304-306]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[307]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[308-309]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[310-311]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[80-81,312-317], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)[48-49,80-81]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)[122,148]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[318]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[319].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[320]. Alterations such as seen here may disrupt TP53 function or expression[321-325].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2021)[245]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[326-328], including sarcomas[329-330]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[331] to 1:20,000[330]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[332]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[226-231]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[226-227]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[333]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[230,232-233]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Atezolizumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is Swissmedic approved as a monotherapy to treat patients with urothelial carcinoma and non-small cell lung cancer (NSCLC). It is also approved in combination with chemotherapy for patients with small cell lung cancer and hepatocellular carcinoma as well as for patients with non-squamous NSCLC without genomic EGFR or ALK tumor aberrations. Atezolizumab is also approved in combination with nab-paclitaxel to treat patients with triple-negative breast cancer whose tumors have PD-L1 expression ≥1%. Please see the drug label for full prescribing information.

GENE ASSOCIATION

CD274 alterations, such as amplification or rearrangements, that lead to overexpression of PD-L1 may predict sensitivity to atezolizumab based on clinical evidence in multiple solid tumor types[64,103,334] . Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to anti-PD-L1 inhibitors such as atezolizumab. Although atezolizumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved overall survival and response to atezolizumab[64,103,334] .

SUPPORTING DATA

In the first-line setting, the Phase 3 IMpower130, IMpower150, and IMpower132 studies have shown that the addition of atezolizumab to chemotherapy-based regimens significantly improves survival for patients with non-squamous NSCLC without EGFR or ALK alterations[335-337] . In IMpower130, median PFS (7.0 vs. 5.5 months, HR=0.64) and median OS (18.6 vs. 13.9 months, HR=0.79) were significantly improved with atezolizumab plus nab-paclitaxel and carboplatin relative to chemotherapy alone; benefit was observed irrespective of PD-L1 status[336]. Similarly, IMpower150 reported improved median PFS (8.3 vs. 6.8 months, HR=0.62) and median OS (19.2 vs. 14.7 months, HR=0.78) with the addition of atezolizumab to bevacizumab, paclitaxel, and carboplatin; longer PFS was observed irrespective of PD-L1 status or KRAS mutation[335]. In IMpower132, the addition of atezolizumab to first-line carboplatin or cisplatin with pemetrexed in non-squamous NSCLC increased median PFS (7.6 vs. 5.2 months, HR=0.60) relative to chemotherapy alone[337]. The Phase 3 IMpower110 study of first-line atezolizumab for patients with metastatic non-small cell lung cancer (NSCLC) reported improved median OS (mOS; 20.2 vs. 13.1 months, HR=0.59), median PFS (8.1 vs. 5.0 months), and ORR (38% vs. 29%) compared with chemotherapy for patients whose tumors had high PD-L1 expression and no genomic alterations in EGFR or ALK[338]. The Phase 3 OAK trial comparing atezolizumab with docetaxel for patients with previously treated NSCLC reported a significant increase in mOS (13.8 vs. 9.6 months) and duration of response (16.3 vs. 6.2 months)[339], confirming previous Phase 2 trial data[64,340] . In the OAK trial, improved OS was observed for patients, regardless of histology (HR=0.73 for squamous and non-squamous) or PD-L1 status, although greater benefit was reported for patients with high PD-L1 tumor cell (>50%) or tumor-infiltrating immune cell (>10%) expression (HR=0.41) compared with those possessing <1% expression on either cell type (HR=0.75)[339]. Retrospective analyses of the OAK trial also identified clinical benefit for patients receiving atezolizumab and metformin compared with atezolizumab alone (ORR of 25% vs. 13%)[341], and for patients with 2 or more mutations in DNA damage response and repair pathway genes compared with those without (durable clinical benefit rate of 57% vs. 31%, p=0.003)[342]. The Phase 3 IMpower010 study of adjuvant atezolizumab treatment following adjuvant chemotherapy for patients with resected Stage II-IIIA NSCLC reported improved median disease-free survival compared with best supportive care (42.3 vs. 35.3 months, HR=0.79), with the greatest benefit observed for patients with PD-L1 tumor cell expression of ≥1% (not reached vs. 35.3 months, HR=0.66)[343]. In the randomized Phase 2 CITYSCAPE study of treatment-naive advanced NSCLC, the addition of tiragolumab to atezolizumab showed clinically meaningful improvement in ORR (37% [25/67] vs. 21% [14/68]) and PFS (5.6 vs. 3.9 months, HR=0.58), with greater ORR (66% [19/29] vs. 24% [7/29]) and PFS (not reached vs. 4.1 months, HR=0.30) observed for patients with PD-L1 tumor proportion scores (TPS) ≥50%[344].

Durvalumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

AREAS OF THERAPEUTIC USE

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is Swissmedic approved to treat patients with non-small cell lung cancer (NSCLC). It is also approved in combination with chemotherapy for patients with small cell lung cancer (SCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as durvalumab based on clinical evidence in multiple solid tumor types[64,66-70,103,334,345-349] . Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-L1-blocking antibodies such as durvalumab. Although durvalumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved overall survival and response to the similar PD-L1-blocking antibody atezolizumab[64,103,334] .

SUPPORTING DATA

In the Phase 3 PACIFIC trial for patients with Stage 3 unresectable non-small cell lung cancer (NSCLC) who did not have progression on chemoradiotherapy, durvalumab monotherapy improved PFS versus placebo across PD-L1 expression subgroups; median PFS (mPFS) was 23.9 versus 5.6 months (HR=0.49) for patients with PD-L1 expression ≥1% and 10.7 versus 5.6 months (HR=0.79) for patients with PD-L1 expression <1%. Median OS (mOS) benefit was observed for patients with PD-L1 expression ≥1% (57.4 vs. 29.6 months, HR=0.60), but not for those with PD-L1 expression <1% (33.9 vs. 43.0 months, HR=1.05)[350-351] . In the Phase 3 ARCTIC study for patients with metastatic NSCLC who had progressed on 2 or fewer prior therapies, single-agent durvalumab improved OS (11.7 vs. 6.8 months, HR=0.63) and PFS (3.8 vs. 2.2 months, HR=0.71) versus the investigator's choice of standard of care (SOC) for patients in cohort A (PD-L1 ≥25%)[352]. However, durvalumab plus tremelimumab did not significantly improve OS (11.5 vs. 8.7 months, HR=0.80) or PFS (3.5 vs. 3.5 months, HR=0.77) compared with SOC for patients in cohort B (PD-L1 <25%)[352]. In the Phase 3 MYSTIC trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC and PD-L1 expression ≥25%, neither durvalumab monotherapy nor durvalumab plus tremelimumab improved OS versus chemotherapy (HR=0.76 vs. HR=0.85); however, patients with blood tumor mutational burden (bTMB) ≥20 Muts/Mb showed improved OS for durvalumab plus tremelimumab versus chemotherapy (21.9 vs. 10.0 months, HR=0.49)[353]. In the Phase 3 POSEIDON trial for patients with treatment-naive EGFR- or ALK-negative metastatic NSCLC, the addition of durvalumab and tremelimumab to chemotherapy improved mOS (14.0 vs. 11.7 months, HR=0.77) and mPFS (6.2 vs 4.8 months, HR=0.72) versus chemotherapy[354]. In Phase 2 trials for patients with advanced or relapsed NSCLC, improved ORR[355-356] and OS[355] for durvalumab monotherapy corresponded with increased tumor cell PD-L1 positivity; patients with very high PD-L1 expression (≥90%) had an ORR of 31% (21/68) compared with ORRs of 16% (24/146) for patients with ≥25% and 7.5% (7/93) for patients with <25% PD-L1 positivity[356]. Re-treatment with durvalumab for patients with PD-L1-positive (≥25%) EGFR-negative or ALK-negative advanced NSCLC who had progressed following previous disease control resulted in a PR or SD for 25% (10/40) of patients[357].

Nivolumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby reducing inhibition of the antitumor immune response. It is Swissmedic approved in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, classical Hodgkin lymphoma (cHL), stomach adenocarcinoma, and esophageal or gastroesophageal junction (GEJ) carcinoma. Furthermore, nivolumab is approved to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). It is also approved in combination with cabozantinib to treat RCC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s) and may predict sensitivity to nivolumab. In various advanced solid tumors, including melanoma, lung, kidney, prostate, and colorectal cancer, PD-L1 expression correlated positively with PD-1 (on lymphocytes) and PD-L2 expression as well as with objective response to nivolumab[75,358] .

SUPPORTING DATA

For patients with platinum-refractory non-squamous non-small cell lung cancer (NSCLC), nivolumab improved median OS (mOS; 12.2 vs. 9.4 months) and ORR (19% vs. 12%) compared with docetaxel in the Phase 3 CheckMate 057 study; PD-L1 expression was associated with OS benefit from nivolumab in this study (HR=0.40-0.59)[99]. In advanced squamous NSCLC, second-line nivolumab resulted in longer mOS (9.2 vs. 6.0 months) and higher ORR (20% vs. 9%) than docetaxel in the Phase 3 CheckMate 017 study; PD-L1 expression was neither prognostic nor predictive of nivolumab efficacy[98,100] . Pooled analysis of CheckMate 057 and CheckMate 017 showed improved long-term OS and PFS benefit for nivolumab over docetaxel, with 5-year OS rates of 13% versus 2.6% (HR=0.68) and PFS rates of 8.0% versus 0% (HR=0.79)[359]. In the CheckMate 227 study, the combination of nivolumab and platinum-based doublet chemotherapy did not improve OS over chemotherapy alone (18.3 vs. 14.7 months, HR=0.81)[360], despite Phase 1 results in the same setting suggesting improved ORR and OS[361]. In the Phase 3 CheckMate 816 study, the combination of nivolumab and platinum-based doublet chemotherapy did show benefit as a neoadjuvant treatment for patients with resectable NSCLC, reporting a pathological CR (pCR) rate of 24% versus 2.2% for chemotherapy alone, and the benefit was consistent across subgroups stratified by PD-L1 expression, stage of disease, or tumor mutational burden (TMB)[362]. A Phase 1 study of nivolumab combined with the immunostimulatory therapy bempegaldesleukin for immunotherapy-naive patients with NSCLC reported an ORR of 60% (3/5; 2 CRs) and mPFS of 18.0 months[363].

Pembrolizumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is Swissmedic approved as a monotherapy for patients with microsatellite-instability-high (MSI-H) or mismatch-repair-deficient (dMMR) colorectal cancer, endometrial carcinoma, gastric carcinoma, and small intestine or bile duct carcinoma. Pembrolizumab is also approved as a monotherapy for patients with classical Hodgkin lymphoma, urothelial carcinoma, melanoma, primary mediastinal large B-cell lymphoma (PMBCL), and head and neck squamous cell carcinoma (HNSCC) whose tumors are expressing PD-L1 with a tumor proportion score (TPS) ≥50%, and for patients with non-small cell lung cancer (NSCLC) who are PD-L1-positive (TPS ≥1%). It is also approved in combination with chemotherapy for patients with non-squamous NSCLC who do not harbor EGFR or ALK mutations, and in combination with chemotherapy for patients with squamous epithelial NSCLC. Additionally, pembrolizumab is approved in combination with axitinib for patients with renal cell carcinoma, and in combination with chemotherapy for HNSCC that is expressing PD-L1. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s) and may predict sensitivity to pembrolizumab. Treatment with pembrolizumab has resulted in a lasting CR in a patient with CD274-amplified DLBCL[364] and in a lasting PR in a patient with CD274-amplified cancer of unknown primary[71]. PD-L1 expression is associated with significantly prolonged median OS for patients with EGFR/ALK wildtype advanced NSCLC treated with pembrolizumab compared with chemotherapy[365-367] . One trial in patients with melanoma observed an improved objective response rate (51% vs. 6%) and PFS (12 vs. 3 months) for PD-L1 positive compared to PD-L1 negative tumors[368]. Furthermore, PD-L1 expression correlated positively with expression of PD-1 (on lymphocytes) and PD-L2, as well as with objective response to the anti-PD-1 antibody nivolumab in various advanced solid tumors[75].

SUPPORTING DATA

The superiority of pembrolizumab over platinum chemotherapy as first-line treatment for patients with PD-L1-positive non-small cell lung cancer (NSCLC) lacking EGFR or ALK alterations was demonstrated in the Phase 3 KEYNOTE-042 and -024 studies, which reported improved median OS (mOS) for PD-L1 tumor proportion scores (TPS) ≥1% (16.7 vs. 12.1 months, HR=0.81)[365] and ≥50% (26.3 vs. 13.4 months, HR=0.62-0.69)[369], with estimated 5-year OS rates of 32% versus 16% in the KEYNOTE-024 study[369]. In the Phase 1b KEYNOTE-100 study of pembrolizumab, mOS was numerically higher for patients with NSCLC and PD-L1 TPS ≥50% relative to those with lower levels of PD-L1 expression in both the first-line (35.4 vs. 19.5 months) and previously treated (15.4 vs. 8.5 months) settings[370]. A retrospective study showed that among patients with NSCLC and high PD-L1 expression treated with first-line pembrolizumab, mOS was improved for patients with TPS of 90-100% relative to those with TPS of 50-89% (not reached vs. 15.9 months, HR=0.39)[371]. Phase 3 studies showed that the addition of pembrolizumab to chemotherapy is superior to chemotherapy alone in the first-line setting for patients with either non-squamous (KEYNOTE-189)[372] or squamous (KEYNOTE-407)[373-374] NSCLC, regardless of PD-L1 or tumor mutational burden (TMB) status[40]. An exploratory analysis of KEYNOTE-189 demonstrated the superiority of the pembrolizumab combination therapy, regardless of blood TMB (bTMB) status[375]. For the first-line treatment of patients with NSCLC and high PD-L1 expression (TPS ≥50%), a meta-analysis of KEYNOTE-024 and -189 reported the combination of pembrolizumab and chemotherapy to be non-superior to pembrolizumab alone in terms of survival benefit; however, the combination did increase ORR (+22%, p=0.011)[376]. In the Phase 2/3 KEYNOTE-010 study, pembrolizumab extended mOS relative to docetaxel (10.4-12.7 vs. 8.2 months) for patients with previously treated PD-L1-positive NSCLC[367]. Multiple clinical trials have demonstrated the efficacy of pembrolizumab, both as a single agent and in combination with chemotherapy, to treat patients with NSCLC and brain metastases[377-379] . Clinical activity has also been achieved with pembrolizumab in combination with the AXL inhibitor bemcentinib[380], the anti-CTLA-4 antibody ipilimumab[381], the anti-TIGIT antibody vibostolimab[382], the HDAC inhibitor vorinostat[383], the multikinase inhibitor lenvatinib[384], and the PARP inhibitor niraparib[385].

Avelumab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 in order to enhance antitumor immune responses. It is Swissmedic approved to treat patients with Merkel cell carcinoma and urothelial carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

CD274 alterations, such as amplification or rearrangement, may lead to overexpression of PD-L1 and predict sensitivity to PD-L1-blocking antibodies such as avelumab based on clinical evidence in multiple solid tumor types[64,103,334,345-348] . Amplification of PDCD1LG2, which is often co-amplified with CD274, may lead to PD-L2 overexpression and predict sensitivity to PD-L1-blocking antibodies such as avelumab. Although avelumab does not block the interaction between PD-L2 and PD-1, clinical evidence in multiple solid tumor types suggests that PD-L2 expression may correlate with improved overall survival and response to the similar PD-L1-blocking antibody atezolizumab[64,103,334] .

SUPPORTING DATA

In the Phase 3 JAVELIN Lung 200 study for patients with advanced non-small cell lung cancer (NSCLC) previously treated with platinum therapy, avelumab did not improve median OS (mOS) when compared with docetaxel (11.4 vs. 10.6 months; HR=0.87) for patients with PD-L1 expression in ≥1% of tumor cells; a prespecified exploratory analysis at higher PD-L1 expression cutoffs showed improved mOS for PD-L1 ≥50% (13.6 vs. 9.2 months; HR=0.67) and ≥80% (17.1 vs. 9.3 months; HR=0.59)[386], and improved 2-year OS rates of 30% versus 21% (≥1% PD-L1), 36% versus 18% (≥50% PD-L1), and 40% versus 20% (≥80% PD-L1)[387]. A post-hoc analysis of this study suggested that a relatively high proportion of patients in the docetaxel arm received subsequent immune checkpoint inhibitor treatment, which may have confounded the outcomes of this study[388]. A Phase 1 study evaluating single-agent avelumab to treat patients with advanced NSCLC reported an ORR of 20%, median PFS (mPFS) of 4.0 months, and mOS of 14.1 months in the first-line setting[389]. A Phase 2 study of avelumab with axitinib to treat advanced NSCLC reported an ORR of 32% (13/41) and mPFS of 5.5 months; tumor reduction was observed for PD-L1-negative and -positive (≥1% PD-L1) samples[390]. A Phase 1b/2 study of avelumab combined with the anti-semaphorin 4D antibody pepinemab to treat advanced NSCLC reported an ORR of 24% (5/21) and DCR of 81% for immunotherapy-naive patients, and ORR of 6.9% (2/29) and DCR of 59% for patients who had disease progression on prior immunotherapy treatment[391]. A study of neoadjuvant avelumab plus chemotherapy to treat early-stage resectable NSCLC reported an ORR of 27% (4/15), which was not considered an enhancement over chemotherapy alone[392].

Cemiplimab

Assay findings association

CD274 (PD-L1)
amplification

PDCD1LG2 (PD-L2)
amplification

AREAS OF THERAPEUTIC USE

Cemiplimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is Swissmedic approved to treat patients with cutaneous squamous cell carcinoma (CSCC) as a monotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification of CD274 or PDCD1LG2 may lead to overexpression of PD-1 ligand(s). In multiple cancer types, PD-L1 expression correlated positively with PD-1 (on lymphocytes) and PD-L2 expression as well as improved clinical benefit in response to anti-PD-1 immunotherapies[74-75,102,358,367-368,393-394] and may predict sensitivity to cemiplimab.

SUPPORTING DATA

The Phase 3 EMPOWER-Lung 1 trial for treatment-naive advanced non-small cell lung cancer (NSCLC) reported that cemiplimab improved median PFS (mPFS, 8.2 vs. 5.7 months, hazard ratio [HR]=0.54), median OS (mOS, not reached vs. 14.2 months, HR=0.57), and ORR (39% vs. 20%) compared with chemotherapy in patients with high PD-L1 expression (TPS ≥ 50%); improved mPFS (6.2 vs. 5.6 months, HR=0.59), mOS (22.1 vs. 14.3 months, HR=0.68), and ORR (37% vs. 21%) were also reported for cemiplimab over chemotherapy in the intention-to-treat population[395]. In a Phase 2 trial of cemiplimab-containing regimens as second-line therapy for NSCLC, cemiplimab combined with ipilimumab elicited a numerically higher ORR (46% [5/11]) compared with high-dose (11% [1/9]) and standard-dose cemiplimab monotherapy (0% [0/8])[396].

Nivolumab + Ipilimumab

Assay findings association

CD274 (PD-L1)
amplification

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby reducing inhibition of the antitumor immune response, and ipilimumab is a cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. The combination is Swissmedic approved in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), and pleural mesothelioma. Furthermore, nivolumab is approved in combination with ipilimumab to treat mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence for PD-L1 overexpression across various solid tumor types, alterations that lead to activation of CD274 may predict sensitivity to combination nivolumab and ipilimumab[31,73,95,397-398] .

SUPPORTING DATA

The Phase 3 CheckMate 227 study of nivolumab plus ipilimumab for patients with advanced non-small cell lung cancer (NSCLC) reported improved median OS relative to chemotherapy (17.1 vs. 13.9 months, HR=0.73) regardless of PD-L1 positivity, histology, tumor mutational burden (TMB) status, or brain metastases[41,399-400] , despite earlier analysis of this trial that suggested improved PFS only for patients with TMB ≥10 Muts/Mb (as measured by this assay)[27]. Similar results were observed in the Phase 3 CheckMate 9LA study, which reported significantly improved 2-year OS (38% vs. 26%), median PFS (6.7 months vs. 5.3 months), and ORR (38% vs. 25%) for patients treated with nivolumab plus ipilimumab in combination with chemotherapy when compared with patients treated with chemotherapy alone[401].

NOTE Genomic alterations detected may be associated with activity of certain drugs approved by applicable regulatory authorities (for example, the FDA, EMA, or country specific regulatory authorities), however the agents listed in this report may have little or no evidence in the patient's tumor type. In addition, the above list is not meant to be a complete and exhaustive list of available therapies. The therapies listed in this report are limited to pharmaceutical drug products and the therapies listed may not be a complete and exhaustive list of available pharmaceutical drug products. This report does not include medical devices, which may be approved for treatment in the particular patient indication. In addition, there may be therapies available which are neither a pharmaceutical product nor a medical device, e.g. rather a treatment method, surgical procedure or a cell therapy and similar methods which may not be subject to approval by the applicable regulatory authorities. There may be pharmaceutical products available which are not authorized by certain applicable regulatory authorities. The therapies approved by applicable regulatory authorities (for example, the FDA, EMA, or country specific regulatory authorities) in other tumor types listed in this report may not be complete and exhaustive because these may not be linked to a specific gene defect or because they were only authorized for other indications. The basis for the search of approved drugs may not be up-to date or may not be accurate. In addition, search errors when searching the therapies cannot be ruled out completely. All treatment decisions remain the full and final responsibility of the respective treating physician. Foundation Medicine's genetic test and this genetic test report, including the information on therapies contained in this report, should not be used as the single basis for the therapy decision. The description of the approved indication in this report is a summary and does not include the exact wording of the approved indication. It is the responsibility of the treating physicians to check the exact indication of any approved label/SmPC/prescribing information for any therapy available in the respective country.

NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. The clinical trials to consider listed in this report may not be complete and exhaustive or may include trials in which the patient cannot participate. Please keep in mind that the information available in the public domain is continually updated and should be investigated by the physician or research staff. There may also be compassionate use programs where patients could be included, and these programs are not listed in this report. The clinical trial information may not be up to date or may not be accurate. In addition, search errors when searching the clinical trials cannot be ruled out completely.

GENE

CD274 (PD-L1)

ALTERATION

amplification

RATIONALE

CD274 (PD-L1) amplification or rearrangements that disrupt the 3' UTR may promote PD-1 signaling and inhibit the antitumor immune response. Antibodies that block the interaction of PD-L1 and PD-1 (alone or in combination with anti-CTLA-4) may therefore be beneficial to release the antitumor immune response. Furthermore, JAK2 inhibitors may be relevant, because they may reduce PD-L1 expression.

NCT04294810

PHASE 3

A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer

TARGETS
PD-L1, TIGIT

LOCATIONS: Bern (Switzerland), Basel (Switzerland), St. Gallen (Switzerland), Lausanne (Switzerland), Monza (Italy), Milano (Italy), Rozzano (Italy), Stuttgart (Germany), Orbassano (Italy), Loewenstein (Germany)

NCT03906071

PHASE 3

Phase 3 Study of Sitravatinib Plus Nivolumab vs Docetaxel in Patients With Advanced Non-Squamous NSCLC

TARGETS
PD-1, AXL, KIT, DDR2, VEGFRs, PDGFRA, TRKA, MET, FLT3, RET, TRKB

LOCATIONS: Bern (Switzerland), Winterthur (Switzerland), Lausanne (Switzerland), Genève (Switzerland), Strasbourg (France), Immenstadt (Germany), Monza (Italy), Milano (Italy), Dijon Cedex (France), Alessandria (Italy)

NCT04385368

PHASE 3

Phase III Study to Determine the Efficacy of Durvalumab in Combination With Chemotherapy in Completely Resected Stage II-III Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-L1

LOCATIONS: Zürich (Switzerland), Lausanne (Switzerland), Strasbourg Cedex (France), Monza (Italy), Orbassano (Italy), Maastricht (Netherlands), Villejuif Cedex (France), Hasselt (Belgium), Leuven (Belgium), Bruxelles (Belgium)

NCT03924869

PHASE 3

Efficacy and Safety Study of Stereotactic Body Radiotherapy (SBRT) With or Without Pembrolizumab (MK-3475) in Adults With Medically Inoperable Stage I or IIA Non-Small Cell Lung Cancer (NSCLC) (MK-3475-867/KEYNOTE-867)

TARGETS
PD-1

LOCATIONS: Zuerich (Switzerland), Geneva (Switzerland), Innsbruck (Austria), Heidelberg (Germany), Modena (Italy), Firenze (Italy), Paris (France), Linz (Austria), Montpellier (France), Essen (Germany)

NCT04026412

PHASE 3

A Study of Nivolumab and Ipilimumab in Untreated Patients With Stage 3 NSCLC That is Unable or Not Planned to be Removed by Surgery

TARGETS
PD-1, PD-L1, CTLA-4

LOCATIONS: Zuerich (Switzerland), Basel (Switzerland), St.Gallen (Switzerland), Lausanne (Switzerland), Monza (Italy), Kempten (Germany), Milano (Italy), Stuttgart (Germany), Dijon (France), Brescia (Italy)

NCT03620669

PHASE 2

1st Line Durvalumab in PS 2 NSCLC Patients

TARGETS
PD-L1

LOCATIONS: Thun (Switzerland), Aarau (Switzerland), Bern (Switzerland), Baden (Switzerland), Fribourg (Switzerland), Basel (Switzerland), Winterthur (Switzerland), St. Gallen (Switzerland), Chur (Switzerland), Bellinzona (Switzerland)

NCT04619797

PHASE 2

A Study of Tiragolumab in Combination With Atezolizumab Plus Pemetrexed and Carboplatin/ Cisplatin Versus Pembrolizumab Plus Pemetrexed and Carboplatin/Cisplatin in Participants With Previously Untreated Advanced Non-Squamous Non-Small Cell Lung Cancer

TARGETS
PD-L1, TIGIT, PD-1

LOCATIONS: Aarau (Switzerland), Chur (Switzerland), Strasbourg (France), Bergamo (Italy), Brescia (Italy), Genova (Italy), Mainz (Germany), Bologna (Italy), Liège (Belgium), Firenze (Italy)

NCT03965468

PHASE 2

Immunotherapy, Chemotherapy, Radiotherapy and Surgery for Synchronous Oligo-metastatic NSCLC

TARGETS
PD-L1

LOCATIONS: Bern (Switzerland), Zurich (Switzerland), Lausanne (Switzerland), Geneva (Switzerland), Maastricht (Netherlands), Rotterdam (Netherlands), Barcelona (Spain), Valencia (Spain), Madrid (Spain), Granada (Spain)

NCT03645928

PHASE 2

Study of Autologous Tumor Infiltrating Lymphocytes in Patients With Solid Tumors

TARGETS
PD-1

LOCATIONS: Bern (Switzerland), Basel (Switzerland), Lausanne (Switzerland), Dresden (Germany), London (United Kingdom), Barcelona (Spain), Lübeck (Germany), Bristol (United Kingdom), Santander (Spain), Madrid (Spain)

NCT03110107

PHASE 1/2

First-In-Human Study of Monoclonal Antibody BMS-986218 by Itself and in Combination With Nivolumab in Patients With Advanced Solid Tumors

TARGETS
CTLA-4, PD-1

LOCATIONS: Zurich (Switzerland), Lausanne (Switzerland), Rozzano (Italy), Siena (Italy), Essen (Germany), Gent (Belgium), Dresden (Germany), Amsterdam (Netherlands), Barcelona (Spain), Napoli (Italy)

GENE
MAP2K1 (MEK1)

RATIONALE
Activating mutation or amplification of MAP2K1 may predict sensitivity to MEK or ERK inhibitors.

ALTERATION
amplification - equivocal

NCT03337698

PHASE 1/2

A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)

TARGETS
PD-L1, MEK, CEA, CXCR4, EZH2, MDM2, ADORA2A

LOCATIONS: Dijon (France), Marseille (France), Montpellier (France), Toulouse (France), Saint Herblain (France), Sutton (United Kingdom), London (United Kingdom), Barcelona (Spain), Pamplona (Spain), Valencia (Spain)

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, ROS1, AXL, TRKA, MET, TRKC, MEK, AKTs, EGFR, PD-L1, KIT, DDR2, VEGFRs, PDGFRA, FLT3, RET, TRKB

LOCATIONS: Maidstone (United Kingdom), Colchester (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Southampton (United Kingdom), Oxford (United Kingdom), Leicester (United Kingdom), Bristol (United Kingdom), Birmingham (United Kingdom), Exeter (United Kingdom)

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: Sutton (United Kingdom), London (United Kingdom)

NCT04185831

PHASE 2

A MolEcularly Guided Anti-Cancer Drug Off-Label Trial

TARGETS
PD-L1, MEK, mTOR

LOCATIONS: Gothenburg (Sweden), Uppsala (Sweden)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT03600701

PHASE 2

Atezolizumab and Cobimetinib in Treating Patients With Metastatic, Recurrent, or Refractory Non-small Cell Lung Cancer

TARGETS
PD-L1, MEK

LOCATIONS: New Hampshire, District of Columbia, Michigan, Virginia, Ohio, North Carolina, Alabama, Florida, Oklahoma

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Massachusetts, New York, Pennsylvania, Maryland, Virginia, Michigan, Ohio, Illinois, Wisconsin, North Carolina

NCT05054374

PHASE 1/2

A Study of Mirdametinib on Its Own or in Combination With Fulvestrant in People With Solid Tumor Cancer

TARGETS
MEK, ER

LOCATIONS: New York, New Jersey

NCT04534283

PHASE 2

A Basket Trial of an ERK1/2 Inhibitor (LY3214996) in Combination With Abemaciclib.

TARGETS
ERK1, ERK2, CDK4, CDK6

LOCATIONS: Indiana

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Texas, Nedlands (Australia), Melbourne (Australia), Blacktown (Australia), Randwick (Australia)

GENE
PDCD1LG2 (PD-L2)

ALTERATION
amplification

RATIONALE
PDCD1LG2 (PD-L2) amplification may promote PD-1 signaling and inhibit the anti-tumor immune response. Antibodies that block the interaction of PD-L2 and PD-1 may therefore be beneficial to release the anti-tumor immune response. Furthermore, JAK2 inhibitors may be relevant, because they may reduce PD-L2 expression.

NCT04294810

PHASE 3

A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer

TARGETS
PD-L1, TIGIT

LOCATIONS: Bern (Switzerland), Basel (Switzerland), St. Gallen (Switzerland), Lausanne (Switzerland), Monza (Italy), Milano (Italy), Rozzano (Italy), Stuttgart (Germany), Orbassano (Italy), Loewenstein (Germany)

NCT03906071

PHASE 3

Phase 3 Study of Sitravatinib Plus Nivolumab vs Docetaxel in Patients With Advanced Non-Squamous NSCLC

TARGETS
PD-1, AXL, KIT, DDR2, VEGFRs, PDGFRA, TRKA, MET, FLT3, RET, TRKB

LOCATIONS: Bern (Switzerland), Winterthur (Switzerland), Lausanne (Switzerland), Genève (Switzerland), Strasbourg (France), Immenstadt (Germany), Monza (Italy), Milano (Italy), Dijon Cedex (France), Alessandria (Italy)

NCT04385368

PHASE 3

Phase III Study to Determine the Efficacy of Durvalumab in Combination With Chemotherapy in Completely Resected Stage II-III Non-small Cell Lung Cancer (NSCLC)

TARGETS
PD-L1

LOCATIONS: Zürich (Switzerland), Lausanne (Switzerland), Strasbourg Cedex (France), Monza (Italy), Orbassano (Italy), Maastricht (Netherlands), Villejuif Cedex (France), Hasselt (Belgium), Leuven (Belgium), Bruxelles (Belgium)

NCT03924869

PHASE 3

Efficacy and Safety Study of Stereotactic Body Radiotherapy (SBRT) With or Without Pembrolizumab (MK-3475) in Adults With Medically Inoperable Stage I or IIA Non-Small Cell Lung Cancer (NSCLC) (MK-3475-867/KEYNOTE-867)

TARGETS
PD-1

LOCATIONS: Zuerich (Switzerland), Geneva (Switzerland), Innsbruck (Austria), Heidelberg (Germany), Modena (Italy), Firenze (Italy), Paris (France), Linz (Austria), Montpellier (France), Essen (Germany)

NCT04026412

PHASE 3

A Study of Nivolumab and Ipilimumab in Untreated Patients With Stage 3 NSCLC That is Unable or Not Planned to be Removed by Surgery

TARGETS
PD-1, PD-L1, CTLA-4

LOCATIONS: Zuerich (Switzerland), Basel (Switzerland), St.Gallen (Switzerland), Lausanne (Switzerland), Monza (Italy), Kempten (Germany), Milano (Italy), Stuttgart (Germany), Dijon (France), Brescia (Italy)

NCT03620669

PHASE 2

1st Line Durvalumab in PS 2 NSCLC Patients

TARGETS
PD-L1

LOCATIONS: Thun (Switzerland), Aarau (Switzerland), Bern (Switzerland), Baden (Switzerland), Fribourg (Switzerland), Basel (Switzerland), Winterthur (Switzerland), St. Gallen (Switzerland), Chur (Switzerland), Bellinzona (Switzerland)

NCT04619797

PHASE 2

A Study of Tiragolumab in Combination With Atezolizumab Plus Pemetrexed and Carboplatin/ Cisplatin Versus Pembrolizumab Plus Pemetrexed and Carboplatin/Cisplatin in Participants With Previously Untreated Advanced Non-Squamous Non-Small Cell Lung Cancer

TARGETS
PD-L1, TIGIT, PD-1

LOCATIONS: Aarau (Switzerland), Chur (Switzerland), Strasbourg (France), Bergamo (Italy), Brescia (Italy), Genova (Italy), Mainz (Germany), Bologna (Italy), Liège (Belgium), Firenze (Italy)

NCT03965468

PHASE 2

Immunotherapy, Chemotherapy, Radiotherapy and Surgery for Synchronous Oligo-metastatic NSCLC

TARGETS
PD-L1

LOCATIONS: Bern (Switzerland), Zurich (Switzerland), Lausanne (Switzerland), Geneva (Switzerland), Maastricht (Netherlands), Rotterdam (Netherlands), Barcelona (Spain), Valencia (Spain), Madrid (Spain), Granada (Spain)

NCT03645928

PHASE 2

Study of Autologous Tumor Infiltrating Lymphocytes in Patients With Solid Tumors

TARGETS
PD-1

LOCATIONS: Bern (Switzerland), Basel (Switzerland), Lausanne (Switzerland), Dresden (Germany), London (United Kingdom), Barcelona (Spain), Lübeck (Germany), Bristol (United Kingdom), Santander (Spain), Madrid (Spain)

NCT03110107

PHASE 1/2

First-In-Human Study of Monoclonal Antibody BMS-986218 by Itself and in Combination With Nivolumab in Patients With Advanced Solid Tumors

TARGETS
CTLA-4, PD-1

LOCATIONS: Zurich (Switzerland), Lausanne (Switzerland), Rozzano (Italy), Siena (Italy), Essen (Germany), Gent (Belgium), Dresden (Germany), Amsterdam (Netherlands), Barcelona (Spain), Napoli (Italy)

GENE
PTEN

ALTERATION
loss exons 1-7

RATIONALE
PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

NCT04380636

PHASE 3

Phase 3 Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)

TARGETS
PD-L1, PARP, PD-1

LOCATIONS: Epagny Metz Tessy (France), Milano (Italy), Rozzano (Italy), Modena (Italy), Udine (Italy), Florence (Italy), Toulon (France), Marseille (France), Bobigny (France), Bad Berka (Germany)

NCT04475939

PHASE 3

Placebo-controlled Study Comparing Niraparib Plus Pembrolizumab Versus Placebo Plus Pembrolizumab as Maintenance Therapy in Participants With Advanced/Metastatic Non-small Cell Lung Cancer

TARGETS
PD-1, PARP

LOCATIONS: Milano (Italy), Stuttgart (Germany), Orbassano (TO) (Italy), Heidelberg (Germany), Gauting (Germany), Muenchen (Germany), Grenoble cedex 9 (France), Legnago (VR) (Italy), Frankfurt (Germany), Pisa (Italy)

NCT03739710

PHASE 1/2

Platform Trial of Novel Regimens Versus Standard of Care (SoC) in Non-small Cell Lung Cancer (NSCLC)

TARGETS
CTLA-4, ICOS, PD-1, TIM-3, PARP

LOCATIONS: Milano (Italy), Orbassano (TO) (Italy), Heidelberg (Germany), Gauting (Germany), Parma (Italy), Ravenna (Italy), Meldola (FC) (Italy), Maastricht (Netherlands), Villejuif Cedex (France), Paris Cedex 05 (France)

NCT03334617

PHASE 2

Phase II Umbrella Study of Novel Anti-cancer Agents in Patients With NSCLC Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy.

TARGETS
PD-L1, PARP, mTORC1, mTORC2, ATR, CD73, STAT3

LOCATIONS: Esslingen a.N. (Germany), Innsbruck (Austria), Heidelberg (Germany), Salzburg (Austria), Köln (Germany), Villejuif (France), Paris (France), Wien (Austria), Bordeaux (France), Nantes Cedex 1 (France)

NCT04276376

PHASE 2

Efficacy and Safety of the Combination of Rucaparib (PARP Inhibitor) and Atezolizumab (Anti-PD-L1 Antibody) in Patients With DNA Repair-deficient or Platinum-sensitive Solid Tumors

TARGETS
PD-L1, PARP

LOCATIONS: Villejuif (France)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Villejuif (France), Saint Herblain (France), Sutton (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Withington (United Kingdom), Massachusetts, New York, Seoul (Korea, Republic of), Seongnam-si (Korea, Republic of)

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, ROS1, AXL, TRKA, MET, TRKC, MEK, AKTs, EGFR, PD-L1, KIT, DDR2, VEGFRs, PDGFRA, FLT3, RET, TRKB

LOCATIONS: Maidstone (United Kingdom), Colchester (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Southampton (United Kingdom), Oxford (United Kingdom), Leicester (United Kingdom), Bristol (United Kingdom), Birmingham (United Kingdom), Exeter (United Kingdom)

NCT03673787

PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

NCT03907969

PHASE 1/2

A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers

TARGETS
PARP, DNA-PK

LOCATIONS: London (United Kingdom), Newcastle upon Tyne (United Kingdom), Connecticut, Texas

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: London (United Kingdom), Copenhagen (Denmark), Manchester (United Kingdom), Newcastle Upon Tyne (United Kingdom), Massachusetts, Rhode Island, New York, Toronto (Canada), North Carolina, Tennessee

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

BRAF T332I	***CDH1*** E781Q	***CREBBP*** R1081C	***MAP3K13*** E774Q
NOTCH1 V1739M	***NOTCH2*** K2121N	***PRDM1*** amplification	***PRKCI*** I374L
RB1 S707del	***ROS1*** amplification	***SDHA*** amplification	***SPEN*** A2013T

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an ncRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER GENOMIC SIGNATURES

Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details: http://www.pathologie.usz.ch/FOne-CDx.aspx.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: The association of a therapy with a genomic alteration or signature does not necessarily indicate pharmacologic effectiveness (or lack thereof); no association of a therapy with a genomic alteration or signature does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness).

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Genomic signatures and gene alterations detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each genomic signature or gene alteration. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X,

"MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	**%CV***
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, CBL, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively

determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

MR Suite Version 5.2.0

The median exon coverage for this sample is 979x

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